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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HAMA, JOANNE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 09/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/620,148	YOSHIHARA, YOSHIHIRO	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/763,117.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/30/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's preliminary amendment filed on July 14, 2003 has been entered. Claims 1-5 are pending and under consideration in the instant action.

This Application is a continuation of US Patent Application No. 09/763,117, now abandoned, submitted on February 15, 2001 as a national phase application of International Patent Application No. PCT/JP99/04439, filed August 18, 1999. This Application also claims foreign priority to a Japanese patent application, 232817/1998, filed August 19, 1998. A WEST search identified a European patent application (Application number 99938511.5, filed August 18, 1999), of which no priority was claimed.

Drawings

New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because Figures 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14 are dark and details in the images are difficult to see. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

DETAILED ACTION

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-2 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1-2 are directed to a "transgenic animal." "Transgenic animal" encompasses a human being, which is non-statutory matter. The claims should be limited and amended as, "non-human."

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for WGA expressed in a mouse, does not reasonably provide enablement for a "trans-synaptic tracer protein" in a "transgenic animal". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification teaches one skilled in the how to make a transgenic mouse, wherein the mouse expresses wheat germ agglutinin (WGA) mRNA, under the control of the L7 or the OMP promoter. In the case of the L7 promoter, WGA mRNA is expressed in Purkinje cells. WGA protein was detected in the deep cerebellar nuclei, the vestibular nucleus, and the Purkinje cells. In the case of the OMP promoter, protein was detected in the vomeronasal organ and nerve bundles thereof. The claims are limited to that which has been taught in the specification. Thus, since the specification has only taught how to make and use the L7 and the OMP promoter driving expression of WGA mRNA in the mouse, the claims are only enabled for the L7 and OMP promoter, driving WGA mRNA in the mouse. Nothing in the specification has taught how to make and/or use any "transgenic animal" (claims 1 and 2) other than mouse. While the specification has taught other examples of trans-synaptic tracer proteins, including, " Concanavalin A agglutinin, Pisum Sativum agglutinin (PSA), Lens Culinaris agglutinin (LCA) and the like (page 3, fourth full paragraph, lines 1-3)," the specification has not taught how to make and/or use these proteins in a transgenic animal. Claims 1 and 2 are to specific expression in neurons. However, the specification has not taught how to make and/or use promoters, other than T7 and OMP, to drive expression in neurons.

The specification states, "the present invention will be further described in the following example. The example is provided for illustrative purposes only, and is not intended to limit the scope of the invention (page 5, third full paragraph)." However, the according to the art at the time of filing, the production of transgenic animals was

unpredictable. The specification teaches that pronuclear injection is one way of producing transgenic mice (page 7, first full paragraph, lines 1-3). However, according to Mullins and Mullins (1996, J. Clin. Invest, 97: 1557-1560), pronuclear injection, the method used to generate transgenic nonmurine animals, is unreliable, as there is low efficiency of gene integration (page 1557, second column, first full paragraph, lines 7-8). Furthermore, Mullins and Mullins state that the major problem regarding pronuclear microinjection is, "that the exogenous DNA integrates randomly into chromosomal DNA. Position effects, where the transgene is influenced by its site of integration in the host chromosome, can have major consequences on the expression of the transgene, including loss of cell specificity, inappropriately high copy number--independent expression and complete silencing of the transgene (page 1557, column 2, second paragraph, line1 to page 1558, first column, first paragraph, lines 1-6)." It should be pointed out that Mullins and Mullins' review was written with a mammalian scope in mind. According to the specification, the invention can be applied to "any animal having neural pathways (page 3, sixth paragraph)." However, pronuclear injection, the method described in the specification, does not work in non-mammalian species such as amphibians, fish, reptiles, birds and insects.

Producing transgenic animals is unpredictable for another reason. This has to do with the selection of the promoter. Claims 1 and 2 can be read broadly to suggest that the method can be applied to any neural promoter. However, characterization of the promoter is a lengthy process. Goswami et al. (2003, Journal of Molecular Evolution, 57:44-51) teach some of the analyses used to characterize a promoter. Goswami et al.

show by 5' deletion analysis that BD2, a greater 5' deletion of the TGF-β5 promoter than BD3, has more activity than BD3, suggesting that the 5' deletion in BD2 uncovered a negative regulator in the promoter (page 46, column 2, first paragraph, lines 3-7). Goswami et al. also show that while there is this difference in promoter activity between the two constructs transfected in XTC cells (*Xenopus* tadpole cell line), there is no difference in the activity of the promoters when transfected in A6 cells (*Xenopus* adult kidney fibroblast cell line). This result suggests that there is a difference in the transcriptional factors between the cell types (page 46, column 2, first paragraph, lines 7-10). Goswami et al. also show that there is a difference in promoter regulation, depending what animal species that promoter is from and into which cells the reporter construct is transfected. TGF-β5, which is found in rats and frogs, was found to be regulated differently. *Xenopus* TGFβ-5 transfected into *Xenopus* cells had activity; it had little to no activity when transfected into mammalian cells (page 47, column 2, section headed "Basal Promoter Activites of TGFβ1 and TGF-β5 Promoter in Mammalian Cell Lines", see also Figures 3 and 4).

As illustrated by Goswami, selecting a regulatory region of a gene as a promoter is not intuitive and requires extensive characterization. This is undue experimentation. One skilled in the art cannot define a regulatory region of a gene as a promoter and expect that another skilled in the art would select the same sequence without guidance.

For these reasons, the specification has not taught how to reliably produce any transgenic animal expressing a trans-synaptic protein, specifically in neural cells. The scope of the claims is limited to only what was taught by the specification. Thus, claims

1 and 2 are not enabled since the specification does not teach how to make and use any transgenic animals, other than mouse. Furthermore, the claims are not enabled for any neural cells, other than the ones that express trans-synaptic protein, under the control of the L7 or OMP promoter.

Claim 3, which depends on claim 1, is not enabled.

Claims 4-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 4 is to a method for screening neuromimetic substances, comprising of administering a test substance to the transgenic animal of claim 1 and selecting a neuromimetic substance, using the trans-synaptic protein expressed in neurons of the transgenic animal as an indicator. Claim 5 is to a neuromimetic substance obtained from the screen of claim 4.

The specification states that "the transgenic animal of the present application is useful for the elucidation of causes for various neurogenic diseases and the establishment of medical treatment for these diseases (page 4, second paragraph, lines 1-3). However, claim 4 is not enabled because nothing in the specification teaches one skilled in the art how to determine whether or not a test substance has an effect on a neuron via monitoring its expression of trans-synaptic protein. The specification does

not describe any assays nor is there a description of how the neurons will be monitored to determine the effect of the neuromimetic substance.

Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The final Written Description Examination guidelines that were published on January 5, 2001 (66 FR 1099; available at http://www.uspto.gov/web/menu/current.html#register).

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

The specification does not adequately describe what a "neuromimetic substance" is. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants effective filing date.

Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). In the instant case, Applicants have not taught what defines a "neuromimetic substance." It is unclear whether the "neuromimetic substance" is a chemical or a protein. It is unclear what structures or physical features a "neuromimetic substance" has to qualify one as such. It is unclear what biological responses a "neuromimetic substance" should have. Nothing in the specification teaches one skilled in the art how to identify what a "neuromimetic substance" is and how to discriminate a group of "neuromimetic substances" from each other. The skilled artisan cannot envision all the possible variant chemical compounds and proteins used to illicit a response in a neuron, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method used. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of identifying it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only stating that "neuromimetic substances" will be isolated using the transgenic animal described in the specification does not meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 is confusing because it can be read as a gene, in the form of mRNA, encoding a trans-synaptic tracer protein, is injected into neurons of a transgenic animal. Alternatively, if a gene is in the form of DNA, a gene cannot direct expression of itself without a promoter, in a cell. To be operable, a gene must be driven by a promoter. If the expression is in neurons, a neural-specific promoter should be used. Claims 2-4 depend from claim 1.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 5 is rejected under 35 U.S.C. 102(b) as being anticipated by Curzon, et al. (1997, Trends in Pharmacological Science, 18: 21-25) or Elias, et al. (1998, Neuron, 21: 1375-1385).

Claim 5 is a product by process claim. According to MPEP 2113:

"Product-By-Process Claims are not limited to the manipulations of the recited steps, only the structure implied by the steps. [E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted) (Claim was directed to a novolac color developer. The process of making the developer was allowed. The difference between the inventive process and the prior art was the addition of metal oxide and carboxylic acid as separate ingredients instead of adding the more expensive pre-reacted metal carboxylate. The product-by-process claim was rejected because the end product, in both the prior art and the allowed process, ends up containing metal carboxylate. The fact that the metal carboxylate is not directly added, but is instead produced in-situ does not change the end product.)"

Claim 5 is to a neuromimetic substance. One example of a neuromimetic substance is D-Fenfluramine, a drug cited to work at influencing the activity of 5-HT

transmitter systems and alter feeding behavior (Curzon et al., page 21, second column, second paragraph, lines 1-3). While D-Fenfluramine is a chemical, another neuromimetic is leptin, a protein. Leptin receptors are highly localized in hypothalamic cell groups, especially in the mediobasal hypothalamus. It is thought that leptin may activate sympathetic preganglionic neurons through a neuronal relay originating in the hypothalamus (Elias, et al., page 1375, second column, second paragraph, lines 13-20). In these situations, D-Fenfluramine and Leptin anticipate a "neuromimetic substance," in claim 5.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is (571) 272-2911. The examiner can normally be reached on Monday-Friday 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, Ph.D. can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JH

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